U.S. Department of Health & Human Services
National Institutes of Health
National Institute on Alcohol Abuse and Alcoholism

Alcohol Alert

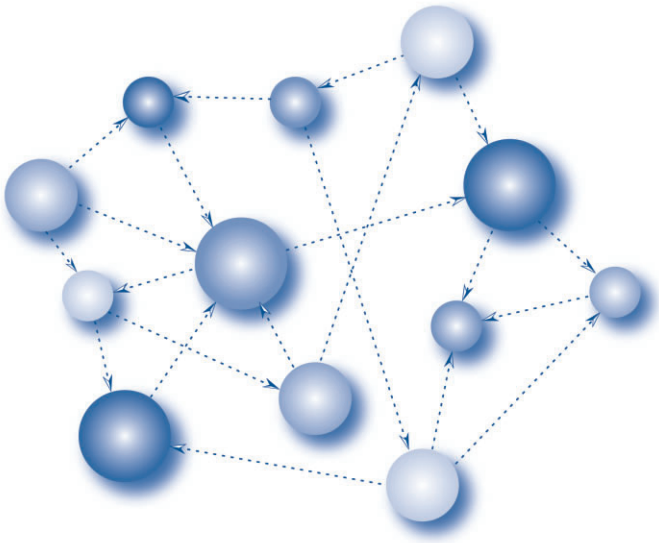
Number 75 April 2008

Systems Biology: *The Solution to Understanding Alcohol-Induced Disorders?*

In 2001, scientists finally cracked the code that reveals the complete genetic blueprint of the human body (the human genome) (1,2). With this genetic blueprint in hand, they hoped to be able to better understand and treat illnesses that affect millions of people worldwide, such as lung diseases, diabetes, cancer, obesity, Alzheimer's disease, and alcoholism (3).

The new map of the human genome has provided researchers with enormous amounts of information about how the body works on a molecular level, which already has led to great progress in understanding how the body functions in health and illness. However, many questions, particularly about complex diseases such as alcoholism, remain unanswered.

The human genome catalogs the distinct genetic parts of the human body, but it does not reveal the intricate ways in which these parts and others (such as transcriptome, proteome, metabolome, etc. [see below for definitions of these terms]) function together. To understand such complex phenomena as alcohol addiction, it is not enough to understand how individual molecules—for example, those involved in communication networks in the brain—interact, or even how they are affected by alcohol. Instead, scientists also must understand how a system of these molecules—for example, the brain as a whole—functions. How do other influences such as alcohol exposure produce their complex effects on and far-reaching consequences for the body? Systems biology is a new field that makes use of advanced technology to explore how the parts of the human body work together, in health and disease, as a synchronized whole.



Systems biology is especially relevant to alcoholism, a multifaceted disease that involves many interrelated and interacting mechanisms. Systems biology approaches provide tools that can help researchers better understand how alcohol affects various body tissues and how the resulting changes lead to the development of addiction to alcohol and organ damage. This new information also has the potential to help researchers develop better and more targeted medications for alcohol-induced disorders (3). This *Alcohol Alert* describes how systems biology might be applied to alcohol research. It examines this innovative approach and suggests ways in which it can lead to practical, targeted treatment interventions for alcoholism.

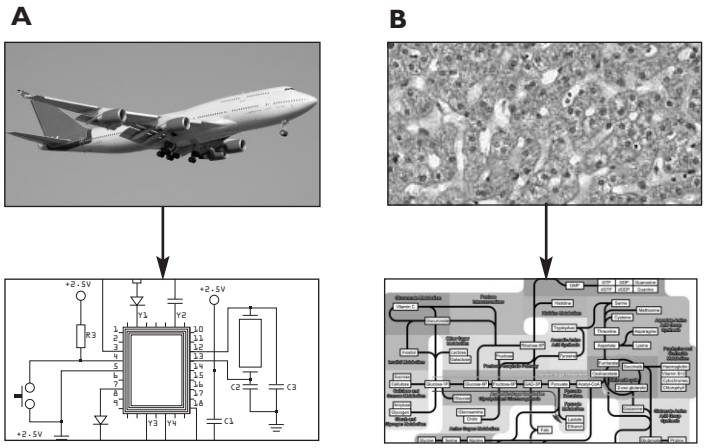
> *"Systems biology is a new field that makes use of advanced technology to explore how the parts of the human body work together, in health and disease, as a synchronized whole."*

What Is Systems Biology?

How is a systems biology approach different from approaches scientists have used in the past? Traditionally, researchers have focused on individual molecules and their interactions. Systems biology's difference—and its advantage—is that it integrates this research to examine larger

systems as a whole. Dr. Hans Peter Fischer (2008) compares the human body to a passenger jet plane (see figure at right) (3). Both consist of many individual parts—whereas the body is made up of billions of individual molecules and cells, a plane may include thousands of screws, cables, wheels, and other diverse elements. Dr. Fischer notes that, although it is not possible to understand the workings of a jet plane without a catalog of these parts, simply identifying them will not describe how a jet plane works. Only by exploring how they interact—how the mechanical parts are connected by wires with electronic components and how flipping one switch affects the movement of different parts—is it possible to understand complex processes such as takeoff, navigation, communication, or landing, or problems with these processes. Similarly, although it is necessary to identify the genes, proteins, and cells that make up the human body, knowing how each part functions will not explain how body systems work or the diseases that affect them. Rather, it is necessary to understand how these parts work together to create complex effects that are larger than the sum of their parts.

Mapping Complex Systems



Like a modern jet plane (A, top), the human body consists of many parts. A technical blueprint for a microchip (A, bottom) catalogues some of the parts in a jet plane, and helps engineers to understand complex processes known as emergent properties—for example, takeoff and landing. Similarly, a map of a human liver cell (B, bottom), catalogues the complex network of biochemical reactions within liver cells (B, top), and helps alcohol researchers understand such emergent properties as detoxification within the liver.

"–Omics" Technologies: The Driving Force Behind Systems Biology

The systems biology approach has been made possible by two developments: the complete sequencing of the human genome and recent technological advances known collectively as "–omics" technologies. These technologies—which most prominently include *genomics*, *proteomics*, and *metabolomics*, described below—enable researchers to study hundreds of samples or molecules in a cell simultaneously.

Genomics approaches are concerned with the activity and function of the complete genetic content (i.e., the genome) of a cell, organ, or organism. One example is the National Institutes of Health (NIH)-sponsored Collaborative Study on the Genetics of Alcoholism (COGA), in which researchers are collecting data from hundreds of families with or without alcoholism (4). COGA will compare hundreds of genes in people with and without alcoholism; the resulting information eventually may allow investigators to identify gene variants that put people at risk for developing alcoholism. Similar studies in laboratory animals that differ in how sensitive they are to alcohol's effects already have identified some DNA regions that may influence the animals' response to alcohol (4).

However, it is important to know not only which gene variants are found in a person but also how active these genes are. Although all cells contain the same set of genetic information, not all genes are active in all cells at the same time. For example, some genes are active only in brain cells, and others only in liver cells. Scientists now can routinely analyze the expression of tens of thousands of genes simultaneously. Such studies already have found that in the brains of alcoholics, the expression of certain genes in various brain regions differs from those in nonalcoholics (4).

"Scientists now can routinely analyze the expression of tens of thousands of genes simultaneously."

Proteomic studies examine the structure and functions of all the proteins[1] found in a cell, organ, or organism. In alcohol research, such

[1] Proteins are large molecules produced from genetic information stored in DNA.

studies can potentially help investigators to understand how chronic alcohol abuse affects the body. For example, in alcoholics, changes in brain function contribute to physical dependence, craving for alcohol, and reduced sensitivity to alcohol's effects (i.e., tolerance). These changes likely occur because certain proteins in the brain are produced at higher or lower levels than normal, allowing the brain to adapt to the constant presence of alcohol in the body. If researchers can identify the proteins that are involved in these processes, it may help them to develop new treatment strategies for alcoholic patients (5).

Metabolomics is the study of small molecules (i.e., metabolites) that are produced when larger molecules, such as proteins and fats, are broken down or transformed into other molecules in the body. The levels of these metabolites change in response to certain signals, both from within the body and from influences outside the body. For example, excessive alcohol use can lead to a disruption in fat metabolism, contributing to the development of early stages of liver disease (i.e., fatty liver) (6). Metabolomic approaches that determine how exactly alcohol interferes with fat metabolism may help researchers develop safe medications to treat these disruptions and the resulting liver disease (6).

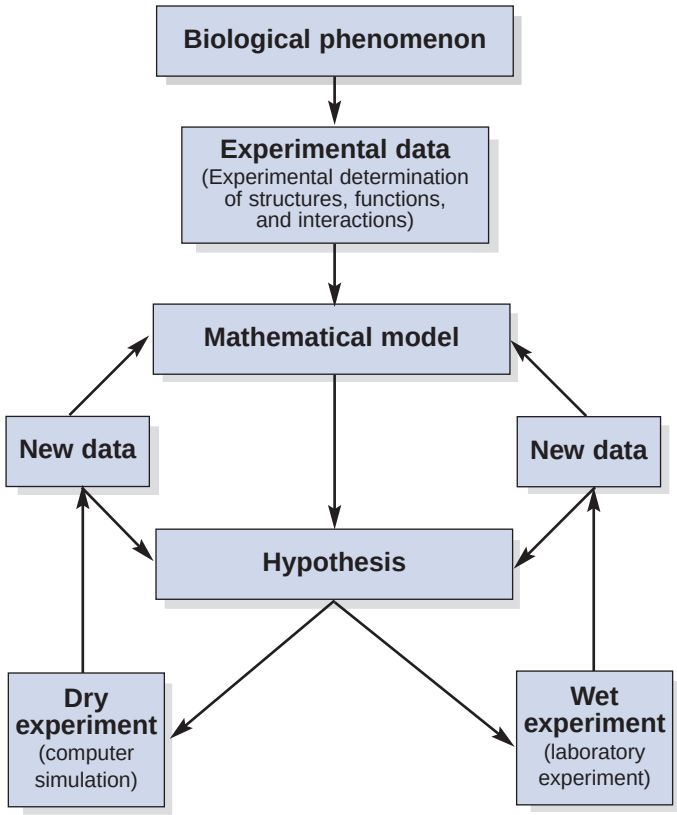
Together, the –omics technologies have allowed researchers in the alcohol field and other areas to gather enormous amounts of information about the workings of the cell on the molecular level. However, –omics technologies also create considerable challenges. Can scientists determine how these diverse and complex systems of genes, proteins, and other "parts" fit together? The answer to this question lies in another integral component of systems biology: the development of mathematical models and computer simulations.

Mathematical Models and Computer Simulations

To interpret the enormous amounts of data generated by –omics technologies, systems biologists can incorporate these data into mathematical equations that model how parts of the cell interact. Using these equations, researchers are attempting to predict how a biological system functions under various conditions, or how it would respond, for example, to a potential new drug. The equations are so complex, however, and the amount of data so extensive, that it generally is not possible to solve them "manually"; instead, researchers use computer simulations, or models, to solve them (3). Computer models are especially useful because they can incorporate data from many types of experiments, including experiments done in test tubes, cell cultures (i.e., groups of cells grown outside of the body), and animal studies (7).

There are several advantages to using computer models. Computer models (or "dry experiments") often are less expensive and time-consuming than biological experiments (or "wet experiments"). Mathematical models from dry experiments can suggest new avenues of research that experimental biologists can then test in new wet experiments. Conversely, theoretical biologists can incorporate the additional data from the new wet experiments to further refine the models (see figure below) (3).

Systems Biology Approaches



Systems biology allows researchers to combine approaches in exploring biological phenomena. Data are integrated into mathematical models that help to generate new ideas (or hypotheses) about how the body works. These hypotheses are tested using both "wet experiments" that take place in the laboratory and "dry experiments," or computer simulations. These experiments generate new data that can help researchers form new hypotheses and refine their mathematical models.

Advantages of a Systems Biology Approach

Systems biology allows scientists to integrate data from different experiments, revealing complex properties that may not be apparent from any single experiment and to integrate and interpret enormous amounts of information about how the human body functions. Systems biology allows researchers to examine body functions on many levels of complexity, from how the body "reads" DNA information to produce various proteins to changes that occur in behavior.

Alcohol and Systems Biology

Drs. Q. Max Guo and Sam Zakhari (2008) observe that "alcoholism is indeed a systems biology disorder" (8). Alcohol exerts complex effects on many levels: individual molecules, cells, and organs, and even a person's behavior. Many of these effects, such as organ damage and alcohol dependence, are the result of a variety of interdependent factors (3). Examining alcohol's effects on only one level (e.g., the molecular level) reveals only a piece of the puzzle. For example, simply examining alcohol's relationship to a single gene or even a group of genes provides only a fragmented view of a complex picture. On the other hand, systems biology gives scientists a means to obtain a more comprehensive picture of how alcohol affects body systems and behavior.

Applications of Systems Biology in Alcohol Research

Modeling alcohol's effects during fetal development—Alcohol consumption by a pregnant woman poses a hazard to the health and development of her unborn child. Depending on the timing and amount of alcohol consumption during pregnancy, the effects on the children range from subtle deficits in brain function (e.g., slight learning disabilities) to a condition called *fetal alcohol syndrome*, which features characteristic facial abnormalities, growth retardation, and brain damage (9). Researchers already have learned a great deal about how maternal alcohol consumption leads to these birth defects. Much of this research has focused on alcohol's effects on the developing brain, such as the formation of new brain cells and the wiring that occurs among these new cells. However, many questions remain—for example, how do different levels of alcohol consumption at different times during pregnancy affect the developing brain? Systems biology approaches may help to fill this knowledge gap (7).

Because researchers cannot directly study alcohol's effects on human fetal development they rely on laboratory animals. Yet the brain structure and development differ between mice, rats, monkeys, and humans. To address these differences, researchers have developed computer models that integrate different types of data on how alcohol affects normal rodent or monkey brain development. Researchers then can compare these models to what is known about fetal brain development in humans, enabling them to translate research findings from other species into information that is useful for pre-

"Systems biology gives scientists a means to obtain a more comprehensive picture of how alcohol affects body systems and behavior."

Systems Biology Lexicon

DNA (deoxyribonucleic acid): The molecule that carries the genetic code in all organisms except some viruses.

Emergent properties: The characteristics of a complex system that arise when various components interact.

Genome: The entirety of all genes of an organism.

Genomics: The study of the structure and function of an organism's complete genetic content, or *genome*.

Metabolite: The intermediary products generated when the body breaks down a particular molecule.

Metabolome: The entirety of all *metabolites* present in a given cell, tissue, or organism.

Metabolomics: The study of small molecules (i.e., *metabolites*) that are produced when larger molecules, such as *proteins* and fats, are broken down or transformed into other molecules in the body.

Protein: The large molecules produced from genetic information stored in *DNA*.

Proteome: The entirety of all *proteins* of a cell, tissue, or organism.

Proteomics: The large-scale study of the structure and functions of *proteins*.

Transcriptome: The entirety of all mRNA molecules (i.e., messenger RNA, the key intermediary between *DNA* and *proteins*) present in a cell, tissue, or organism.

Transcriptomics: The large-scale study of the expression of mRNAs in a given cell, organ, or organism.

dicting alcohol's effects on humans (7). In particular, such models might help researchers determine the effects of even low levels of maternal alcohol consumption on the developing fetus (7).

***Understanding alcoholic lung disease*—**Alcohol abuse has long been known to increase a person's risk of developing pneumonia. However, recent studies found that it also increases a person's risk of a severe form of acute lung injury called *acute respiratory distress syndrome*. Scientists estimate that in the United States, tens of thousands of deaths occur each year from alcohol-related lung injury (10). Systems biology approaches may help researchers to determine how alcohol produces such devastating lung damage. These approaches may be instrumental in identifying the genes and proteins that are altered in the lungs of alcohol-exposed animals as compared with animals that have not been exposed to alcohol (10). Eventually, systems biology approaches may help identify new strategies for treating people with alcoholic lung disease (10).

***Exploring alcohol-related brain disease*—**The brain is particularly vulnerable to excessive alcohol use. Alcoholics often exhibit problems with memory, learning, planning, and other advanced brain functions. In severe cases, they may even develop dementia. To date, systems biology approaches have not been used specifically to study alcohol-related brain disease. However, systems biology studies already have helped expose the mechanisms contributing to other brain disorders, such as Alzheimer's disease. Researchers have identified some genes involved. Systems biology also has helped identify molecules that can be used to more accurately diagnose people with Alzheimer's, even in its early stages (11).

***Enhancing drug discovery and development*—**The traditional process for developing, testing, and obtaining approval for a new drug is time-consuming and expensive—the process can take more than a decade and cost as much as $900 million (12). Researchers expect that systems biology will help to streamline this process, making drug development more efficient. In particular, computer simulations of diseases will allow researchers to use dry experiments to assess the potential safety and effectiveness of new drug candidates. Recently, a number of pharmaceutical companies have begun systems biology programs to support drug discovery and development (13).

At the same time, publicly and privately funded initiatives and consortia have brought together researchers from diverse disciplines—such as biology, genetics, biochemistry, physics, mathematics, computer sciences, statistics, and engineering—to contribute to a systems biology approach to treating disease (3). For example, NIH's new Roadmap for Medical Research includes an initiative on Bioinformatics and Computational Biology, which seeks to create a national software engineering system to allow biomedical researchers to collect and evaluate large amounts of data. This initiative brings together scientists from across the country, enabling them to share and analyze data using a common software system (14).

Conclusion

With the decoding of the human genome, researchers gained access to extensive information about the molecules in the body, how they function in the healthy organism, and how they may contribute to certain diseases. However, despite this wealth of information, many questions remain about the ways in which these molecules interact to control more complex phenomena, including the development of many common disorders. Systems biology offers scientists a promising tool with which to deal with such complexities and may revolutionize the prognosis, diagnosis, and treatment of alcohol use disorders and other multifaceted disorders. These new approaches provide researchers with new opportunities to work together, share data, and use computer technology and mathematical modeling to steer research in exciting new directions.

References

(1) Landers, E.S.; Linton, L.M.; Birren, B.; et al. Initial sequencing and analysis of the human genome. *Nature* 409:860–921, 2001. PMID: 11237011 **(2) Venter, J.C.;** Adams, M.D.; Myers, E.W.; et al. The sequence of the human genome. *Science* 291(5507):1304–1351, 2001. PMID: 11181995 **(3) Fischer, H.P.** Mathematical modeling of complex biological systems: From parts lists to understanding systems behavior. *Alcohol Research & Health* 31(1):49–59, 2008. **(4) Sloan, C.D.;** Sayarath, V.; and Moore, J.H. Systems genetics of alcoholism. *Alcohol Research & Health* 31(1):14–25, 2008. **(5) Hiller-Sturmhöfel, S.;** Sobin, J.; and Dayne Mayfield, R. Proteomic approaches for studying alcoholism and alcohol-induced organ damage. *Alcohol Research & Health* 31(1):36–48, 2008. **(6) Harrigan, G.G.;** Maguire, G.; and Boros, L. Metabolomics in alcohol research and drug development. *Alcohol Research & Health* 31(1):26–35, 2008. **(7) Gohlke, J.M.;** Hiller-Sturmhöfel, S.; and Faustman, E.M. A systems-based computational model of alcohol's toxic effects on brain development. *Alcohol Research & Health* 31(1):76–83, 2008. **(8) Guo, Q.M.;** and Zakhari, S.D. Commentary: Systems biology and its relevance to alcohol research. *Alcohol Research & Health* 31(1): 5–11, 2008. **(9) Stratton, K.;** Howe, C.; and Battaglia, F., eds. *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment.* Washington, D.C.: National Academy Press, 1996. **(10) Kershaw, C.D.;** and Guidot, D.M. Alcoholic lung disease. *Alcohol Research & Health* 31(1):66–75, 2008. **(11) Pasinetti, G.M.;** and Hiller-Sturmhöfel, S. Systems biology in the study of neurological disorders: Focus on Alzheimer's disease. *Alcohol Research & Health* 31(1):60–65, 2008. **(12) Service, R.F.** Surviving the blockbuster syndrome. *Science* 303(5665):1796–1799, 2004. PMID: 15031490 **(13) Mack, G.S.** Can complexity be commercialized? *Nature Biotechnology* 22(10):1223–1239, 2004. PMID: 15470456 **(14) Kantor, L.W.** NIH roadmap for medical research. *Alcohol Research & Health* 31(1):12–13, 2008.

Resources

Source material for this *Alcohol Alert* originally appeared in the issue of *Alcohol Research & Health* that examines the topic of systems biology.

- ***Alcohol Research & Health,* Volume 31, Number 1, 2008. This issue describes the discipline of systems biology and explores how its approaches can benefit alcohol research. Articles highlight the genetics of alcoholism, the study of metabolomics and proteomics, and the use of mathematical modeling in systems biology. Other articles show how scientists are putting systems biology approaches into practice in the study of alcohol-related disease.**

Full-text articles from each issue of *Alcohol Research & Health* are available on the NIAAA Web site at http://www.niaaa.nih.gov.

Subscriptions to *Alcohol Research & Health* are available from the Superintendent of Documents for $25. Write to New Orders, Superintendent of Documents, P.O. Box 371954, Pittsburgh, PA 15250–7954; or fax 202/512–2250.

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES

NIAAA Publications Distribution Center
Attn.: *Alcohol Alert*
P.O. Box 10686
Rockville, MD 20849–0686

Official Business
Penalty for Private Use $300

PRSRT STD
POSTAGE AND FEES PAID
NIH/NIAAA
PERMIT NO. G-824